REMARKS

Claims 1-9 are pending in the present application.

The rejection of Claims 1-9 under 35 U.S.C. §103(a) over Ferrari et al (EP 0015418) and Virno (EP 0118940) in combination with Berge et al (J. Pharm. Sci. 1977) is respectfully traversed.

The claimed invention relates to a novel salt of L-(-)-moprolol with L-(+)-tartrate in a 2:1 molar ratio (Claim 1), as well as compositions containing the same and methods for making the same. The Examiner alleges that the claimed invention is obvious in view of Ferrari et al when viewed together with Virno and Berge et al. Applicants submit that the cited art fails to disclose or suggest this salt and request reconsideration of this ground of rejection.

Ferrari et al is cited as disclosing the preparation of the L-(+) glutamate salts of L-(+)-moprolol and L-(-)-moprolol. Virno is cited as disclosing a composition containing L-(-)-moprolol hydrochloride. Although the Examiner recognizes that neither Ferrari et al nor Virno disclose a tartrate salt of L-(-)-moprolol, the Examiner cites Berge et al, which discloses "many potentially useful pharmaceutically acceptable salts, such salts include the chloride and tartrate of the organi base (p 2, table 1). Based on the foregoing alleged disclosures, the Examiner merely concludes that "it would have been obvious to a person having ordinary skill in the art to substitute from among the known pharmaceutically acceptable salts, which include chloride and glutamate, as well as tartrate, in order to obtain a composition having the most desirable pharmacological efficacy and/or ease of administration."

The Examiner is reminded that a proper obviousness analysis involves a three-step process. First, Office personnel should establish a *prima facie* case of unpatentability considering the factors set out by the Supreme Court in *Graham v. John Deere.* See, e.g., *In re Bell*, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993) ("The PTO bears the burden of establishing a case of *prima facie* obviousness."); *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), requires that to make out a case of obviousness, one must:

(A) determine the scope and contents of the prior art;

(B) ascertain the differences between the prior art and the claims in issue;

(C) determine the level of skill in the pertinent art; and

(D) evaluate any evidence of secondary considerations.

Indeed, the Supreme Court in *KSR* reiterated that the framework for the objective analysis for determining obviousness under 35 U.S.C. §103 is stated in *Graham* v. *John Deere Co.*, which is set forth above. Further, the Office has set forth its "Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.*" in Federal Register, Vol. 72, No. 195, 57526-57535, which clearly has not been complied with in the current action.

Moreover, the Examiner is reminded that "the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness." *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) Applicants submit that the Office has failed to establish a *prima facie* case of obviousness.

Moreover, Applicants submit that the problem of the present invention can be described as that of providing a novel pharmaceutical composition for ophthalmic use

comprising a salt of L-(-)-moprolol having a better local tolerability than the hydrochloride (see page 1, lines 14-15, page 2, lines 3-8). The solution of the present invention can be described as that of using a novel salt of L-(-)-moprolol with L-(+)-tartrate in a 2:1 molar ratio, i.e., two moles of L-(-)-moprolol per mole of L-(+)-tartrate.

Indeed, the Examiner is correct that neither Ferrari et al nor Virno disclose a tartrate salt of L-(-)-moprolol. Further, neither Ferrari et al nor Virno disclose a tartrate salt of L-(-)-moprolol having the claimed molar ratio. Berge et al. do not disclose or suggest selection of L-(+)-tartrate. Berge et al. only discloses tartrate salts within a list of 80 salts (Table I lists 53 potentially useful salts and Table II lists 27 potentially useful salts).

Perhaps more importantly, Berge et al do not represent an expectation of success even if tartrate were selected. Berge et al merely represents a historical statistical analysis of salt forms approved by the FDA, as well as those that have not been approved, and a salt selection guide. Berge et al do not suggest using specifically tartrate, much less suggest how this salt would behave. There remains no expectation of which salt would be best for a particular compound, much less what properties each salt form would have. Thus, while Berge et al does suggest that any number of salts is approved by the FDA (53 appear in Table 1), Applicants respectfully disagree with the characterization that tartrate would have been an obvious substitution. Rather, what Berge et al actually teaches is that among all of the FDA salts, hydrochloride and sulfate salts are the ones to use since they constitute a major portion of all salts that the FDA has approved, 42.98 % for hydrochloride (i.e., the salt of Virno) and 7.46% for sulfate.

Therefore, what we have here is Ferrari et al and Virno suggesting the use of a glutamate salt or a hydrochloride salt, respectively, without any direction to select a tartrate salt and Berge et al providing little more that an interesting historical statistical analysis of

FDA-approved drugs. If the Examiner or the artisan wished to glean anything from Berge et al following the Examiner's logic, it would be that they would choose salts in the following order: (1) hydrochloride, (2) sulfate, (3) bromide, and (4) chloride. Certainly this does not put tartrate at the top of the list or even provide adequate motivation to select tartrate salts, much less provide any expectation of success in so choosing.

Even if the Examiner were to look past the clear suggestion in Berge et al that would direct the artisan away from the tartrate salt as claimed, at best, the combined disclosures of Ferrari et al, Virno, and Berge et al would constitute an "invitation to experiment" or could be viewed as making it "obvious to try" to arrive at the present invention. However, "obvious to try" has long been held *not* to constitute obviousness. *In re O'Farrell*, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995).

Some allege that *KSR* eliminates the "obvious to try" defense, but this is not the case. *KSR* clearly states that "obvious to try" may constitute obviousness, but only under certain circumstances. Specifically, *KSR* stated that the fact that a claimed combination of elements was "obvious to try" might show that such combination was obvious under 35 U.S.C. § 103, since, if there is design need or market pressure to solve problem, and there are finite number of identified, predictable solutions, person of ordinary skill in art has good reason to pursue known options within his or her technical grasp, and if this leads to anticipated success, it is likely product of ordinary skill and common sense, not innovation. However, the Examiner offers nothing to show how these factors apply and whether there would be such an expectation or anticipated success.

The fact of the matter remains, there must be some reasonable expectation of success. To this end, "the prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success." *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants submit that there is nothing in the combination of Ferrari et al, Virno, and Berge et al which provide any reasonable suggestion for the claimed invention, much less any reasonable expectation of success.

Indeed, Ferrari et al, Virno, and Berge et al do not disclose or suggest the choice of a 2:1 molar ratio. On the contrary, Berge et al states that "those [salts] of dicarboxylic acid confer water solubility if one carboxylic group is left free" (page 2, right column, 6-9 lines from the bottom). Such a disclosure would actually teach away from a 2:1 molar ratio. To this end, the Examiner is reminded that MPEP §2141.02 states: "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Accordingly, even if the artisan would have combined the cited references as the Examiner alleges, he would not have arrived at the claimed invention.

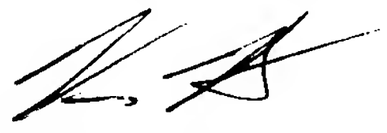
It should be further noted that Virno was cited in the specification at page 1, lines 9-13. Applicants compared the hydrochloride salt of Virno with the salts of the present invention in Example 1 (see pages 3-5 of the specification). Example 1 clearly shows better results in terms of tolerability of the (2:1) L-(-)-moprolol L-(+)-tartrate salt. This result is not predicable by reviewing the combined disclosures of Ferrari et al, Virno, and Berge et al.

In view of the foregoing, withdrawal of this ground of rejection is requested.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



Vincent K. Shier, Ph.D.
Registration No. 50,552

Customer Number
22850
(703) 413-3000
Fax #: (703)413-2220